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EXAMINER	
WANG, CHUN CHENG	
ART UNIT	PAPER NUMBER
4171	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/563,167	CHANE-CHING, JEAN-YVES	
	Examiner	Art Unit	
	CHUN-CHENG WANG	4171	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/25/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 6 recite 'polyglycine type' (line4) and 'polyacrylic-polyacrylamide type' (line 7) render it indefinite. The addition of the word "type" to an otherwise definite expression (e.g., Friedel-Crafts catalyst) extends the scope of the expression so as to render it indefinite. *Ex parte Copenhaver*, 109 USPQ 118 (Bd. App. 1955). Likewise, the phrase "ZSM-5-type aluminosilicate zeolites" was held to be indefinite because it was unclear what "type" was intended to convey. *Ex parte Attig*, 7 USPQ2d 1092 (Bd. Pat. App. & Inter. 1986).

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. Applicant claims: a colloidal dispersion of calcium phosphate with length 5-500 nm, and thickness 0.5-20 nm, and at least one polymer which complexes calcium (claim 1); length 5-300 nm (claim 2); thickness 0.5-15 nm (claim 3); monetite or apatite structure (claim 4); polymer: carboxylate, phosphate or phosphonate anionic functional group (claim 5); polymer Markush group: polymers with a peptide backbone of polyaspartic acid, polyglutamic acid, polylysine or polyglycine type, homopolymers and copolymers of acrylic acid, methacrylic acid, polyacrylic acid or polymethacrylic acid, copolymers of the polyacrylic-polymethacrylic, polyacrylic-polyhydroxyethylacrylic or polyacrylic-polyacrylamide type, polysaccharide polymers, guar gum, carboxymethylcellulose or xanthan gum, modified polysaccharide polymers having phosphate or phosphonate functional groups, and peptide polymers comprising phosphate functional groups (claim 6); molar ratio of anionic functional group/Ca = 0.0001-0.1 (claim 7); and polymer MW 1000-20000 (claim 8).

6. Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kumta et al (US7247288), in view of Nagata et al. (US5427754).

7. Regarding claims 1-3: Applicant claims: a colloidal dispersion of calcium phosphate with length 5-500 nm, and thickness 0.5-20 nm, and at least one polymer which complexes calcium (claim 1); length 5-300 nm (claim 2); and thickness 0.5-15 nm (claim 3). Kumta et al disclose associating the nanocrystalline calcium phosphate (claim 1) of size smaller than 100 nm (column 5 lines 24-26 and Fig.5) with polymer matrix (claims 13 and 14) and hydroxyapatite complexed with a transforming nucleic acid that is capable of transforming a cell (column 12, lines 31-33).

Deleted: ; and
Deleted: thickness

8. Regarding claim 4: Applicant claims the calcium phosphate has monetite or apatite structure (claim4). Kumta et al. disclose the use of hydroxyapatite, read on apatite, complex with biomaterial (column 4 lines 61-63), and brushite ($CaHPO_4 2H_2O$, read on monetite with water) complex with nucleic acids, proteins, peptides (including antibodies) and pharmacological agents (column 3 lines 50-56.)

9. Kumta et al. disclose nano-structured hydroxyapatite is believed to have several advantages in its use in bone tissue engineering due to its higher surface area and consequently

higher reactivity which offers better cellular response. In addition, nano-sized hydroxyapatite is useful as an effective surface modification agent for binding numerous biological molecules (column 1 lines 44-49.) However, they are silent about the actual size and shape of the nanocrystalline calcium phosphate in their invention.

Nagata et al disclose a plate-like hydroxyapatite, calcium phosphate apatite structure. The size of these crystals varies with the reaction conditions adopted. Generally, it is in the range of approximately 50 to 200 nm (column 2 lines 65-68 and column 3 lines 1-2). Nagata et al also disclose hexagonally platelike (example 2) and rodlike or needlelike (Comparative Experiment 2) microcrystals measuring about 100 nm in maximum length. Although Nagata et al do not disclose the thickness of the microcrystals, the shape of the crystal should put the thickness in the range of instant claims 2 and 3.

It would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to use smaller size crystal, i.e. higher surface area per weight, in the colloidal dispersion.

10. Claims 5-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kumta et al. (US7247288), in view of Wong et al. (US2003/0017189) and Sikes (US5051401 and US4603006).

11. Regarding claims 5, 6 and 8: Kumta et al. further disclose polymers complex calcium phosphate which include polyamino acids (column 9 lines 43-44), such as poly-L-lysine, read on carboxylate functional group (instant claim 6) and peptide backbone of polyaspartic acid, polygumatic acid, polylysine or polyglycine (instant claim 7), non-erodible polymers such as

polyacrylate (column 9 line 48), read on homopolymers of acrylic acid and polyacrylic acid of claim 7, and polysaccharides such as starch (column 9 lines 27-28). Kumta et al do not teach the polymer with phosphate or phosphonate functional groups (instant claim 5), guar gum, carboxymethylcellulose or xanthan gum, modified polysaccharide polymers having phosphate or phosphonate functional groups and peptide polymers comprising phosphate functional group(instant claim 6).

12. Wong et al. disclose a scale-like calcium hydrogen phosphate [0035], read on monetite, in a gel-forming, erodible polymer matrix [0034]. Wong et al also disclose use of polymers complex calcium phosphate in drug release application: acrylamide/sodium acrylate copolymer [0085], swellable polymer comprising cellulosic polymer of sodium carboxyl methyl cellulose and noncellulosics such as polyacrylic acids, natural gums, including guar and starch graft copolymers and the like [0083] , read on xanthan gum, insoluble materials including copolymers of acrylic acid and methacrylic acid esters, methacrylic acid copolymers, ammoniomethacrylate copolymer and polyamides [0090]. Wong does not teach modified polysaccharide polymers having phosphate or phosphonate functional groups and peptide polymers comprising phosphate functional group. It would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to utilize the teaching form the application of calcium phosphate in drug release and combine with teaching from Kumta et al to use the above mentioned polymers that complex calcium phosphate for their intended applications.

13. Sikes discloses a homopolymer having glycosidic linkages between monosaccharides carrying a substituent derived from COOH, PO_4H_2 or SO_4H α or β and/or derivatives thereof

(US4603006, column 5 lines 64-67) to have scale inhibiting properties especially for calcium carbonate scales (column 6 lines 50-53). Sikes also discloses preferred monosaccharide polymers molecular weight range of 2,500-20,000 (column 5, lines 59-62) which is in the range of 1000-20000 (instant claim 8). Sikes fails to teach peptide polymers comprising phosphate functional groups. It would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to use the scales inhibition properties of the phosphorylated polysaccharide to complex with calcium phosphate to have better mechanical strength in their intended applications, for example building material or antirust agent.

14. Sikes discloses in another patent a poly-amino acid compound, polyanionic polypeptide (US5051401, column 2 lines 43 and 44), capable of inhibiting mineral deposition, which has the structure: $Poly(X)_m(Y)_n$ where each X independently is aspartate, glutamate, glutamine, asparagine, or anionic derivatives of these amino acids, or phosphoserine, each Y independently is a phosphorylated amino acid such as phosphoserine, phosphohomoserine, phosphotyrosine, phosphothreonine, phosphoglutamine, phosphoasparagine, or mixtures of these residues (Abstract), read on peptide polymers with phosphate or phosphonate functional groups (instant claim 5 and claim 6), and may serve as inhibitors of dental tartar and plaque formation (column 13 lines 38-39) gelling with carboxymethylcellulose (column 14, EXAMPLE C). Sikes also discloses the polypeptides of his invention could be incorporated into polymeric based controlled released drug delivery matrices for site specific therapy directly into the perianular region of the heart prosthesis (column 15 lines 62-67). Controlled release devices incorporating a phosphonate derivative have been formulated to deliver that drug for more than 30 years without depletion

(column 15 lines 68 and column 16 lines 1-3). Kumta et al. further disclose nano-structured hydroxyapatite is believed to have several advantages in its use in bone tissue engineering due to its higher surface area and consequently higher reactivity which offers better cellular response. In addition, nano-sized hydroxyapatite is useful as an effective surface modification agent for binding numerous biological molecules (column 1, lines 44-50).

It would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to use polyanionic polypeptide calcium phosphate complex as drug controlled release devices that have higher surface area and consequently higher reactivity.

15. Regarding claim 7: Kumta et al. further disclose depending on the ultimate use for the hydroxyapatite complex described herein, the complex can be formulated in a variety of appropriate and effective forms. For example, for topical application of a hydroxyapatite complex to the skin, for oral ingestion, the complex may be formulated into a capsule, tablet, liquid or other suitable dosage form and other dosage forms, such as intravenous, otic, ocular, suppository, transmucosal, subcutaneous or transdermal dosage forms can be prepared in any manner known in the art. For all dosage forms, the hydroxyapatite can be formulated with any suitable excipient (vehicle) as is known, including without limitation, diluents, lubricants, coatings, capsules, emulsifiers, adjuvants, buffers, solvents, matrices, colorants, flavorings, sweeteners, humectants and thickening agents. It would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to formulate the dosage depending on their ultimate use and thus the molar ratio of functional groups in the polymer to calcium in the dispersion.

16. Applicant claims: a colloidal dispersion of calcium phosphate with length 5-500 nm, and thickness 0.5-20 nm, and at least one polymer which complexes calcium (claim 1); dispersion agent (claim 9); which is polyphosphate (claim 10); molar ratio dispersion agent/Ca = 0.001-0.5 (claim 11); doping elements selected from the group consisting of alkaline earth metal elements, rare earth metal elements, and elements with an atomic number of between 57 and 71 (claim 12); and drying (claim 13).

17. Claims 1 and 9-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Itoi et al. (US6159437) in view of Kumta et al. (US7247288).

18. Itoi et al. disclose an apatite dispersion with polymeric phosphate dispersion agents such as sodium hexametaphosphate and sodium tripolyphosphate (column 3 lines 53 and 54) and the size of the apatite particle is 10-100 nm in short-axis and 30-300 nm in long axis (column 3 lines 23-27), i.e. needle, column, rice grain or oval shapes (column 3 lines 22-24). Itoi et al. further disclose the amount of apatite particles in the dispersion media differs according to the use for which it is intended, if the density of the slurry is too low the dispersion effect will be inadequate, and If the density of the slurry is too high, the slurry will become viscous, and the reaggregation will be facilitated due to interaction between the particles after dispersion, and the concentration should be within the range of 0.01 and 80 percent by weight. The molar ratio of 0.2 and 0.5 can be obtained by using 1 wt % of sodium triphosphate with 99 wt % of apatite and 20 wt % of sodium triphosphate with 80 wt % of apatite respectively. Itoi et al. also disclose because hydroxyapatites are zwitterions, the hydroxyapatite derivatives are products in which cations or anions have been partially exchanged or reacted with Ca^{2+} or OH^{-}. Examples of such products include: fluoroapatites, in which fluorine atoms have been substituted for hydroxyl groups; chloroapatites, or carbonated apatites; barium apatites, strontium apatites, or magnesium apatites, in which other alkaline earth metal elements have been substituted for calcium; copper-

substituted apatites, zinc-substituted apatites, or lead-substituted apatites, in which calcium ions have been partially exchanged with divalent metal ions; and others, including silver-substituted apatites, cesium-substituted apatite (read on rare earth metal), etc. Any of these can be obtained by treating hydroxyapatites with appropriate metallic salt solutions or prescribed anionizing agents which exchange ions in aqueous solution (column 3, lines 3-19). Itoi et al. further disclose apatite powder obtained by spray (column 4, line 66). Itoi et al. fail to disclose the polymers that complex calcium and to the molar ratio of dispersion agent to calcium explicitly, which is 0.0001 to 0.5. Kumta et al. disclose a colloidal dispersion of calcium phosphate (claim 1) and polymer which complex calcium (claims 13 and 14). Kumta et al. fail to disclose the requirement of the dimension and dispersion agent, polyphosphate. It would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to mix the colloidal dispersion of calcium phosphate and polymer which complex calcium for their intended use with dispersion agent, polyphosphate, to have better dispersion and minimize the reaggregation of calcium phosphate particles, corporate the metal of desired in aqueous solution then spray drying to obtain apatite powder.

19. Applicant claims: a method to prepare dispersion of calcium phosphate platelets with length 5-500 nm, and thickness 0.5-20 nm, and polymer which complexes calcium i) calcium salt with pH value of 4 to 6; ii) add phosphate solution to solution obtained in step i) over a period of 30 min to 4 hours to obtain Ca/P molar ration of 1 to 2.5 and maintain pH at 4 to 6; iii) heat at 50°C to 95°C; iv) washing the dispersion; v) adding dispersion agent; vi) separating the colloidal dispersion; and the solution in step i) or ii) further comprise ammonium ions, and at lest one polymer which complexes calcium added during step i) or ii) (claim 14); calcium solution is a $CaCl_2$ or $Ca(NO_3)_2$ solution (claim 15); concentration of calcium solution is between 0.25M and 2.5M (claim 16); phosphate solution is ammonium phosphate or sodium phosphate solution (claim 17); Ca/P molar ratio in solution step ii) is between 1.3 and 1.7 (claim 18); heat treatment in step iii) is between 50°C to 95°C (claim 19).

20. Claims 14-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kumta et al. (US7247288) in view of Itoi et al. (US6159437).

21. Kumta et al. disclose hydroxyapatite was chemically synthesized using $CaCl_2$ and Na_3PO_4 in deionized water. Stock reagent solutions were first prepared, including: 2 M calcium solution as required by instant claim 14 step i) and claim 16 (column 18, lines 28 and 29), buffered saline (…1.5 mM Na_3PO_4…) required by instant claim 14 step ii) and claim 17 (column 18, lines 31 and 32). The calcium solution, 20 mMoles, containing plasmid DNA was mixed with Na_3PO_4 solution, 1.5 mMoles, then incubated for either 4 or 12 hours at a pH of 7.5 and temperature of 37°C and the nanocrystalline hydroxyapatite was formed (column 18, lines 18 to 25). The solution was then washed (column 18, lines 41-52). Kumta et al. also disclose a typical protocol includes the steps of adding the $CaCl_2$ solution containing plasmid DNA to the Na_3PO_4 solution in the presence of a water soluble polymer such as polyethylene glycol or PMMA. The resulting mixture can then be air-dried or dried in vacuum to generate the polymeric structure containing the nanosized hydroxyapatite particles (column 22, lines 23- 29). The hydroxyapatite has Ca/P molar ration of 1.67 (column 1, line 29). Kumta also disclose widely used aqueous colloidal precipitation reactions to synthesize hydroxyapatite are as follows:

$$10Ca(OH)_2+6H_3PO_4 \rightarrow Ca_{10}(PO_4)(OH)_2+18H_2O \quad \text{(Formula I)}$$

$$10Ca(NO_3)_2+6(NH)_2HPO_4+2H_2O \rightarrow Ca_{10}(PO_4)_6(OH)_2+12NH_4NO_3+8HNO_3 \quad \text{(Formula II)}$$

Itoi et al. disclose apatite dispersion with polymeric phosphate dispersion agents such as sodium hexametaphosphate and sodium tripolyphosphate (column 3 lines 53 and 54).

Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a

product of the prior art, the claim is unpatentable even though the prior product was made by a different process. *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

"The Patent Office bears a lesser burden of proof in making out a case of *prima facie* obviousness for product-by-process claims because of their peculiar nature" than when a product is claimed in the conventional fashion. *In re Fessmann,* 489 F.2d 742, 744, 180 USPQ 324, 326 (CCPA 1974). Once the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to applicant to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product. *In re Marosi,* 710 F.2d 798, 802, 218 USPQ 289, 292 (Fed. Cir. 1983).

Conclusion

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chun-Cheng Wang whose telephone number is (571)270-5459. The examiner can normally be reached on Monday to Friday w/alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Tarazano can be reached on 571-272-1515. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/D. Lawrence Tarazano/
Supervisory Patent Examiner, Art Unit 4171